

The Office continues to reject Claims 1-9, 12-14, and 17 under USC 35 § 112, first paragraph, for failure to satisfy the written description requirement. This rejection is expanded to include dependent Claims 10, 11, 15, 16, and 18-21 in the instant Office Action. The predominant basis for rejection remains, i.e., the Specification fails to define sequences that confer activity to TnaA and TrpR so that one skilled in the art would recognize possession of TnaA sequences lacking tryptophanase activity or biologically active TrpR sequences.

The Applicants' Response of August 2001, addressed the initial rejection of Claims 1-9, 12-14, and 17 under 35 USC § 112, first paragraph, by citing references disclosed in the Specification that describe the TnaA and TrpR sequences (Deely and Yanofsky, 1981, and Gunsalus and Yanofsky, 1980, respectively). The Office viewed this Response as insufficient and required stipulation of which sequence structures correlate with the intended function of the instant invention.

Regarding the rejection based on failure to disclose "*a nucleic acid sequence which is capable of inactivating the gene encoding a TnaA tryptophanase*" (Claims 1-9), or "*mutated fragments*" of TnaA tryptophanase coding sequence (Claim 12-14); the Applicants hereby, respond by emphasizing that the Specification, as originally filed, describes at Examples 1 and 2, methods whereby, the claimed construct may be prepared. What is more, the Specification describes an "*indole*" test (see page 18, lines 6-13) which would allow one skilled in the art to determine whether a mutation introduced in the gene encoding TnaA tryptophanase is capable of inactivating the gene. The absence of indole would indicate the presence of an inactivated TnaA tryptophanase gene. Hence, by following the methods described and by employing such an indole test, the Applicants have described with sufficient

clarity how one skilled in the art would obtain the nucleic acids which are capable of inactivating the gene encoding the TnaA tryptophanase; particularly a mutated sequence or fragment of the gene encoding an inactivated tryptophanase.

In further support of this Specificational disclosure, the Applicants are pleased to file herewith, a research statement by Laurent CHEVALET, PhD, which demonstrates that any person skilled in the art can generate a sequence of the gene encoding TnaA tryptophanase, or fragment thereof, and test the activity of the expressed mutated tryptophanase obtained in a cell using the "indole test" described on page 18, lines 6-13 of the Specification. The CHEVALET statement provides examples of mutated sequences which contain either a missense stop codon (ICONE 100, see Appendix 1) or replacement of a TnaA gene coding fragment by a TrpR gene (ICONE 200, see Appendix 2). The nature of the mutations carried by ICONE 100 and ICONE 200 are identified in the instant Specification (page 15, Table 1), referenced in citations of the Specification, and explained in the instant statement.

Hence, the Applicants submit that the instant Specification discloses to one skilled in the art, how to obtain and recognize representative *"nucleic acid sequences capable of inactivating the gene encoding a TnaA tryptophanase"*, and *"mutated fragments of TnaA tryptophanase coding sequence"* embraced by the scope of the claims. Reconsideration of the rejection, and withdrawal thereof, is respectfully solicited.

With regard to the Applicants failure to disclose *"biologically active fragments of the TrpR tryptophanase operon"*, the Applicants demonstrate in the aforementioned CHEVALET statement, that a person skilled in the art can make

and identify the representative sequence depicted in Appendix 2 which comprises the nucleic fragment nt 511-837; corresponding to a biologically active fragment of the TrpR gene. This biologically active fragment can be obtained by using the two primers TrpR3 and TrpR4 described on page 19 (lines 1-5) of the Specification.

Since the Applicants do not describe a "test" to determine whether a TrpR gene fragment is biologically active or not, the Applicants respond to the Office rejection by limiting the biologically active fragments, relative to TrpR tryptophanase operon in Claim 17, to *"biologically active fragments obtained by amplification of the coding sequence of the TrpR gene using the pair of primers having the sequences TrpR3 (SEQ ID No. 17) and TrpR4 (SEQ ID No. 18)."* The Applicants submit that the instant Amendment provides positive definition of claimed subject matter, and hereby, obviates the § 112, first paragraph, rejection for lack of written description. Reconsideration of the rejection, and withdrawal thereof, is respectfully solicited.

Finally, the Applicants submit that the instant Response and Amendment obviate any objection to the generic base claims, thereby legitimizing the dependent claims which limit the scope of the base claim.

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Accordingly, entry of the present amendment and research statement, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

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Enclosure: Postal Card Receipt, Amended Claim (Clean and Marked-up Form), CHEVALET research statement, and fee for three (3) month extension.

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**THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.**

#### **CLAIM 17 (marked-up form)**

The first construct of Claim 16, wherein said nucleic acid sequence encoding a molecule which is ribonucleotide or protein in nature, and which acts negatively on the P<sub>trp</sub> promoter, is the sequence encoding the TrpR tryptophan operon aporepressor or **[one of its biologically active fragments]** the biologically active fragment obtained by amplification of the coding sequence of the TrpR gene using the pair of primers having the sequences TrpR3 (SEQ ID No. 17) and TrpR4 (SEQ ID No. 18).

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#### **CLAIM 17 (clean form)**

C The first construct of Claim 16, wherein said nucleic acid sequence encoding a molecule which is ribonucleotide or protein in nature, and which acts negatively on the P<sub>trp</sub> promoter, is the sequence encoding the TrpR tryptophan operon aporepressor or the biologically active fragment obtained by amplification of the coding sequence of the TrpR gene using the pair of primers having the sequences TrpR3 (SEQ ID No. 17) and TrpR4 (SEQ ID No. 18).

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